REMARKS

I. Claim Status

Claims 1-6 and 8 are currently pending. Claims 3-6 remain withdrawn as being directed to non-elected subject matter, and claim 7 was previously cancelled. Claim 1 is amended to delete the term "infection." Applicants reserve the right to file a continuation application directed to the cancelled subject matter.

II. 35 U.S.C. § 112, First Paragraph Rejection

Claims 1, 2, and 8 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing the enablement requirement. (Office Action at 2). In particular, the Office alleges that "the specification, while being enabling for a method for inhibiting the development of severe epilepsy in patients with head trauma, cerebral ischemia and neurosurgical operation with atipamezole, does not reasonably provide enablement for the method of inhibiting the development of epilepsy in other patients with the varied and different types of infections." (Office Action at 3).

Without conceding the propriety of the rejection, and with the sole purpose of advancing prosecution, Applicants have amended claim 1 to delete the term "infection." Accordingly, this rejection is now moot, and Applicants respectfully request its withdrawal.

III. 35 U.S.C. § 103(a) Rejection

Claims 1, 2, and 8 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Puurunen, K. et al., *Neuropharmacology* (2001) 40:597-606 ("Puurunen"), Ginsberg et al., *Stroke* (1989) 20:1627-42 ("Puurunen"), as evidenced by

Leker et al., *Brain Research Reviews*, 42: 187-203 (2003). (Office Action at 7.) Applicants traverse this rejection for the following reasons.

The Office essentially concludes that the present claims are obvious over Puurunen, Ginsburg, and Leker based on inherency. However, as discussed in the Response submitted March 22, 2011, the Office has failed to establish that the combination of Puurunen, Ginsberg, and Leker renders the claims *prima facie* obvious either explicitly *or* inherently.

The Office contends that while "Puurunen does not teach the administration of the drug to human patient at risk of developing epilepsy," Leker "teaches that epileptic seizures may be the result of cerebral ischemia and may also cause brain damage." (Office Action at 8-9.) "Therefore . . . when a patient with brain ischemia is treated with atipamezole, the compound will inherently inhibit the development of epilepsy upon administration." (*Id.* at 9.) Citing *In re Best* and *In re Fitzgerald*, the Office contends that where "the prior discloses subject matter which there is a reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed . . . the burden is shifted to the applicants to 'prove that subject matter shown to be in the prior art does not possess characteristic relied on.'" (*Id.* at 11.)

Applicants respectfully disagree and submit that the Office has not established a *prima facie* case of obviousness. As provided in the recent *Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex* ("2010 PTO Obviousness Guidelines"), the Office must identify reasons "that would have prompted a person of ordinary skill in the relevant field to combine the elements in a way the claimed new invention does' in an obviousness determination." 75 Fed. Reg. 53,643,

53,646 (2010) (citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 83 U.S.P.Q.2d 1169, 1174 (Fed. Cir. 2007)) (quoting *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1731 (2007)). In addition, the Office must show that the prior art references teach or suggest all the claim limitations. *See, e.g.,* M.P.E.P. § 2143.03 (emphasis added) (citing *In re Royka,* 180 U.S.P.Q. 580 (C.C.P.A. 1974)).

Here, the claimed invention as a whole would not have been obvious for at least the reason that the references, whether taken alone or in combination, fail to teach or suggest every element recited in claims. Specifically, Puurunen alone, or in combination with Ginsberg and Leker, fails to teach or disclose a method for inhibiting the development of epilepsy in accordance with the pending claims. As acknowledged by the Office, "Puurunen does not teach the administration of [a selective α_2-adrenoreceptor] to human patient at risk of developing epilepsy." (Office Action at 8.) Applicants respectfully submit that neither Ginsberg nor Leker remedies Puurunen's deficiencies.

Ginsberg merely provides a review on rodent models of global and focal cerebral ischemia "for investigating the mechanisms, prevention, and treatment of ischemic brain injury," and nowhere mentions administering a selective an α_2-adrenoreceptor to human patient at risk of developing epilepsy. While Leker provides a broad review of the potential neuroprotective effects of current anti-epileptic drugs, Leker fails to include any discussion on such effects for α_2-adrenoreceptor antagonists. And, even if Leker had included α_2-adrenoreceptor antagonists in its review, Leker's results are inconclusive and unlikely to lead one of ordinary skill in the direction of the claimed methods. For example, Leker teaches that animal models should be appreciated differently depending

upon whether the model is studying global or focal ischemia, and that with global ischemia, animal studies "should not be taken as proof of neuroprotective capabilities relevant to stroke." (Leker at 190.) Studies pertaining to focal ischemia are "more indicative for the future potential use of a given AED in stroke patients." (*Id.* at 191.)

Despite the Office's conclusion from Ginsberg - that one of ordinary skill in the art would have "extrapolate[d] the results obtained by Puurunen . . . in rats to . . . humans and as such develop a method for treating human patients with brain ischemia with atipamezole" - Leker teaches that one of ordinary skill in the art would not have necessarily made that same conclusion. (Office Action at 9.)

In fact, Leker teaches that studies employing antioxidants and anti-inflammatory agents for cerebral protection have also yielded promising results in laboratory animals but *failed* to produce clinically significant improvements in humans." (Leker at 190.) (emphasis added). Similarly, Puurunen also distinguishes between animal and human stroke patients, suggesting that atipamezole's disclosed effect in rats may not be the same in human patients. (*See* Puurunen at 604.) Thus, one of ordinary skill in the art would have understood that, based on Puurunen, Ginsberg and Leker, extrapolating results from rat models to humans in studying cerebral ischemia is rather unpredictable.

Leker also teaches that a particular anti-epileptic drug's neuroprotective capabilities would have also been unpredictable. For example, clinical studies of fosphenytoin as a neuroprotectant found *no* efficacy in humans with stroke but RCM "showed promise in preventing damage in patients undergoing coronary bypass surgery . . . ." (Leker at 195.) "[O]lder AEDs including CBZ, DPH, VPA, barbituates and newer ones such as LTG probably bestow *no* clinically significant neuroprotective effects."

(*Id.*) (emphasis added). "For FBM, LEV and ZNS, the presently available date are scant and insufficient," and "there is *no* published evidence of their having any efficacy in cerebral ischemia . . . [f]or oxacarbazepine, neurontin and vigabatrin." (*Id.* at 196.) (emphasis added). "In contrast, TGB and TPM have very promising neuroprotective profiles . . . ." (*Id.*) Leker concludes "that currently *no* individual AED can be viewed as a potential sole neuroprotectant against ischemic injury." (*Id.*) (emphasis added).

Thus, the Office has failed to establish that there is any reason to believe that one of ordinary skill in the art, based on Puurunen, Ginsburg, and Leker, would have had any reasonable expectation that when a patient with brain ischemia is treated with atipamezole, the compound will successfully inhibit the development of epilepsy. In fact, as discussed previously, one of ordinary skill in the art would have expected quite the opposite. Atipamezole had been reported to potentiate kainic acid induced convulsion and mortality in rats. (Halonen, T. et al., "α2-Adrenoceptor Agonist, Dexmedetomidine, Protects Against Kainic Acid-Induced Convulsions And Neuronal Damage," *Brain Res.* (1995) 693:217-24.)) Even acknowledged by the Office, that "the state of the prior art . . . teaches that α_2-adrenoceptors antagonist including selective α_2-adrenoceptors antagonist such as atipamezole have proconvulsant effect," it is unclear how the Office arrived at the conclusion that one of ordinary skill in the art would have expected α_2-adrenoceptors such as atipamezole to "inherently inhibit the development of epilepsy upon administration [of atipamezole]." (Office Action at 5.) Consequently, burden shifting under *Best* and *Fitzgerald* is not appropriate here.

As clearly established by case law and the M.P.E.P., "[t]he fact that a certain result or characteristic may occur or be present in the prior art is *not* sufficient to

establish the inherency of that result or characteristic." (M.P.E.P. § 2112) (emphasis added.) Rather, the Office must to show that "the allegedly inherent characteristic necessarily flows from the teachings in the applied prior art." (M.P.E.P. § 2112.) (emphasis in original, citations omitted). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted)

In this case, Puurunen, Ginsburg, and Leker do *not* "make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." Rather, one of ordinary skill in the art would have expected the opposite result and, therefore, would not have been guided to the instantly claimed methods.

For at least this additional reason, the proposed combination of references fails to teach all of the elements of the instant claims and Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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